1: Exp Cell Res 2003 Mar 10;284(1):14-30

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Neuregulins: functions, forms, and signaling strategies.

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The neuregulins (NRGs) are cell-cell signaling proteins that are ligands for receptor tyrosine kinases of the ErbB family. The neuregulin family of genes ha four members: NRG1, NRG2, NRG3, and NRG4. Relatively little is known about the biological functions of the NRG2, 3, and 4 proteins, and they are considered in this review only briefly. The NRG1 proteins play essential roles i the nervous system, heart, and breast. There is also evidence for involvement of NRG signaling in the development and function of several other organ systems, and in human disease, including the pathogenesis of schizophrenia and breast cancer. There are many NRG1 isoforms, raising the question "Why so many neuregulins?" Study of mice with targeted mutations ("knockout mice") has demonstrated that isoforms differing in their N-terminal region or in their epidermal growth factor (EGF)-like domain differ in their in vivo functions. These differences in function might arise because of differences in expression pattern or might reflect differences in intrinsic biological characteristics. While differences in expression pattern certainly contribute to the observed difference in in vivo functions, there are also marked differences in intrinsic characteristic that may tailor isoforms for specific signaling requirements, a theme that will b emphasized in this review.

Publication Types:

- Review
- Review, Academic

PMID: 12648463 [PubMed - indexed for MEDLINE]

1: Curr Opin Neurobiol 2001 Jun;11(3):287-96

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Neuregulin and ErbB receptor signaling pathways in the nervou system.

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The neuregulins are a complex family of factors that perform many functions during neural development. Recent experiments have shown that neuregulins promote neuronal migration and differentiation, and regulate the selective expression of neurotransmitter receptors in neurons and at the neuromuscular junction. They also regulate glial commitment, proliferation, survival and differentiation. At interneuronal synapses, neuregulin ErbB receptors associate with PDZ-domain proteins at postsynaptic densities where they can modulate synaptic plasticity. How this combinatorial network - comprising many neuregulin ligands that signal through distinct combinations of dimeric ErbB receptors - elicits its multitude of biological effects is beginning to be resolved.

Publication Types:
- Review
- Review, Tutorial

PMID: 11399426 [PubMed - indexed for MEDLINE]

1: J Neurosci Res 2000 Apr 15;60(2):237-44 Related Articles, Links

rhGGF2 protects against cisplatin-induced neuropathy in the rat.

ter Laak MP, Hamers FP, Kirk CJ, Gispen WH.

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In many patients treated with cisplatin a peripheral sensory neuropathy develops This side-effect is considered dose-limiting, and therefore restricts the total dose of cisplatin that can be administered. Recent in vitro and in vivo studies suggest that recombinant human Glial Growth Factor 2 (rhGGF2) has neuroprotective effects. This prompted us to investigate in a rat model whether rhGGF2 ameliorates cisplatin neuropathy. A total of 48 rats were randomly divided into four groups of 12 rats each. Three groups received cisplatin and were treated with either 0.1 mg/kg rhGGF2, 0.3 mg/kg rhGGF2 or placebo. The fourth group (saline/placebo) served as age-matched controls. In the cisplatin/placebo treated rats a neuropathy developed, as determined by measurements of the nerve conduction velocity (NCV). Treatment with rhGGF2 dose-dependently protected against the neuropathy. Histological examination and morphometric analysis revealed that rhGGF2 also protects against cisplatin-induced changes in the morphology and size of DRG satellite cell nuclei. In a control study rhGGF2 did not affect normal NCV development. We conclude that rhGGF2 treatment is of benefit in the treatment of cisplatin neuropathy in the rat. Copyright 2000 Wiley-Liss, Inc.

PMID: 10740229 [PubMed - indexed for MEDLINE]

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1: Adv Exp Med Biol 1999;468:283-95

Related Articles, Links

Neuregulin in neuron/glial interactions in the central nervous system. GGF2 diminishes autoimmune demyelination, promotes oligodendrocyte progenitor expansion, and enhances remyelination.

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Marchionni MA, Cannella B, Hoban C, Gao YL, Garcia-Arenas R, Lawso D, Happel E, Noel F, Tofilon P, Gwynne D, Raine CS.

Cambridge NeuroScience Inc., Massachusetts 02139, USA.

Related Resources

Glial growth factor 2 (GGF2) is a neuronal signal that promotes the proliferatio and survival of the oligodendrocyte, the myelinating cell of the central nervous system (CNS). This study has focused on recombinant human GGF2 (rhGGF2) and it's potential to affect clinical recovery and repair to damaged myelin in chronic relapsing experimental autoimmune encephalomyelitis (EAE) in the mouse, a major animal model for the human demyelinating disease, multiple sclerosis (MS). Mice with EAE were treated with rhGGF2 during both the acut and relapsing phases, and GGF2 treatment led to delayed signs, decreased severity and resulted in statistically significant reductions in relapse rate. Further, rhGGF2-treated groups displayed CNS lesions with more remyelinatio than in controls. This correlated with increased expression of myelin basic protein exon 2, a marker for remyelination, and with an increase of the regulatory cytokine, IL-10. Thus, a beneficial effect of a neurotrophic growth factor has been demonstrated upon the clinical, pathologic and molecular manifestations of autoimmune demyelination, an effect that was associated wit increased expression of a Th2 cytokine. rhGGF2 treatment may represent a novel approach to the treatment of MS (Cannella et al., 1998).

PMID: 10635037 [PubMed - indexed for MEDLINE]

1: J Neurosci 1999 Dec 15;19(24):10757-66

Neuregulin induces GABA(A) receptor subunit expression and neurite outgrowth in cerebellar granule cells.

Rieff HI, Raetzman LT, Sapp DW, Yeh HH, Siegel RE, Corfas G.

Division of Neuroscience, Department of Neurology, Children's Hospital and Harvard Medical School, Harvard Medical School, Boston, Massachusetts 02115, USA.

Neuregulin (NRG), a growth and differentiation factor that signals via erbB receptor tyrosine kinases, has been shown to have biological effects in both the CNS and the peripheral nervous system. We report here that erbB4 is expressed in mature cerebellar granule cells, where it appears to be concentrated at the granule cell postsynaptic terminals. We also show that one form of NRG, Ig-NRG, plays a crucial role in aspects of cerebellar granule cell development in vitro. First, Ig-NRG treatment of granule cells in culture selectively induces the expression of the GABA(A) receptor beta2 subunit. This increase in subunit expression is paralleled by an increase in functional GABA(A) receptors. In contrast to its effects on GABA(A) receptor subunit expression, Ig-NRG does not upregulate NMDA receptor N2B and N2C subunit expression. Second, we demonstrate that Ig-NRG also enhances neurite outgrowth from cultured granul cells. Ig-NRG does not, however, act as a survival factor for the granule cells. We have compared the effect of Ig-NRG with the effects of brain-derived neurotrophic factor (BDNF), a neurotrophin that exerts specific effects on granule cells in culture, and found that BDNF does not mimic the effects of Ig-NRG on GABA(A) receptor subunit expression. Our results show that Ig-NRG has specific effects on granule cell development and maturation and may regulate these processes in vivo.

PMID: 10594059 [PubMed - indexed for MEDLINE]

1: FEBS Lett 1999 Mar 26;447(2-3):227-31 Related Articles, Links

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Binding specificities and affinities of egf domains for ErbB receptors.

Jones JT, Akita RW, Sliwkowski MX.

Genentech, Inc., Department of Molecular Oncology, South San Francisco, CA 94080, USA.

ErbB receptor activation is a complex process and is dependent upon the type and number of receptors expressed on a given cell. Previous studies with defined combinations of ErbB receptors expressed in mammalian cells have helped elucidate specific biological responses for many of the recognized gene products that serve as ligands for these receptors. However, no study has examined the binding of these ligands in a defined experimental system. To address this issue, the relative binding affinities of the egf domains of eleven ErbB ligands were measured on six ErbB receptor combinations using a soluble receptor-ligand binding format. The ErbB2/4 heterodimer was shown to bind al ligands tested with moderate to very high affinity. In contrast, ErbB3 showed much more restrictive ligand binding specificity and measurable binding was observed only with heregulin, neuregulin2beta, epiregulin and the synthetic heregulin/egf chimera, biregulin. These studies also revealed that ErbB2 preferentially enhances ligand binding to ErbB3 or ErbB4 and to a lesser degree to ErbB1.

PMID: 10214951 [PubMed - indexed for MEDLINE]

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1: J Exp Med 1998 Oct 19;188(8):1535-9

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Neu differentiation factor (NDF), a dominant oncogene, causes apoptosis in vitro and in vivo.

PubMed Services

Grimm S, Weinstein EJ, Krane IM, Leder P.

Department of Genetics, Harvard Medical School, and the Howard Hughes Medical Institute, Boston, Massachusetts 02115, USA.

Neu differentiation factor (NDF, also called neuregulin) is a potent inducer of epithelial cell proliferation and has been shown to induce mammary carcinomas in transgenic mice. Notwithstanding this proliferative effect, we have shown that a novel isoform of NDF can induce apoptosis when overexpressed. Here we report that this property also extends to other NDF isoforms and that the cytoplasmic portion of NDF is largely responsible for the apoptotic effect, whereas the proliferative activity is likely to depend upon the secreted version of NDF. In accordance with these contradictory properties, we find that tumors induced by NDF display extensive apoptosis in vivo. NDF is therefore an oncogene whose deregulation can induce transformation as well as apoptosis.

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1: Neuron 1997 Jun;18(6):847-55

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Neuregulins and their receptors: a versatile signaling module in organogenesis and oncogenesis.

PubMed Services

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Molecular Neurobiology Program, Skirball Institute, New York University Medical Center, New York 10016, USA.

Publication Types:

- Congresses
- Review
- Review, Tutorial

Related Resources

PMID: 9208852 [PubMed - indexed for MEDLINE]

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Neuregulins and neuregulin receptors in neural development.

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The neuregulins are a family of closely related proteins that play important roles in neural and cardiac development, as well as in mammary carcinogenesis. The pleiotropic activities of these molecules are transduced by a set of receptor protein tyrosine kinases that exhibit structural similarity to the receptor for epidermal growth factor. Recent results have demonstrated essential roles for the neuregulins and their receptors in regulating cell number, determining cell fate, and establishing pattern in the developing central and peripheral nervous systems.

Publication Types:
- Review
- Review, Tutorial

PMID: 9039794 [PubMed - indexed for MEDLINE]

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1: Development 1996 May;122(5):1427-38

Related Articles, Links

Effects of GGF/neuregulins on neuronal survival and neurite outgrowth correlate with erbB2/neu expression in developing rat retina.

Bermingham-McDonogh O, McCabe KL, Reh TA.

Cambridge NeuroScience, Seattle, WA 98195, USA.

We have examined the expression of neuregulin and its putative receptors, erbB2/neu, erbB3 and erbB4/tyro2 during retinal development, and tested several potential functions of this class of molecules in dissociated rat retinal cell cultures. At least one form of neuregulin is expressed in the retina, from the earliest stages of retinal development examined; in addition, all three of the known receptors are expressed by retinal neurons in a developmentally regulate manner. When added to cultures of embryonic or neonatal rat retinal cells, neuregulin (rhGGF2) promotes survival and neurite extension from retinal neurons in a dose-dependent manner. These results indicate that in addition to their well described effects on glia, the neuregulins also have direct effects on central nervous system neurons.

PMID: 8625831 [PubMed - indexed for MEDLINE]

1: Curr Opin Neurobiol 1995 Oct;5(5):606-12

Neuregulins and their receptors.

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The recent identification of an activator for the ErbB2/Neu receptor has uncovered a new family of polypeptide growth factors that undoubtedly play a major role in the regulation of neuronal growth and differentiation. These factors, called the neuregulins, are expressed in neural and mesenchymal tissues and activate members of the epidermal growth factor family of receptor tyrosine kinases. The identification and characterization of the neuregulins and their receptors will facilitate the dissection of the biochemical pathways regulating nervous system development.

Publication Types:
- Review
- Review, Tutorial

PMID: 8580712 [PubMed - indexed for MEDLINE]

Structural and functional aspects of the multiplicity of Neu differentiation factors.

Wen D, Suggs SV, Karunagaran D, Liu N, Cupples RL, Luo Y, Janssen AM, Ben-Baruch N, Trollinger DB, Jacobsen VL, et al.

Amgen, Inc., Thousand Oaks, California 91320.

We used molecular cloning and functional analyses to extend the family of Neu differentiation factors (NDFs) and to explore the biochemical activity of different NDF isoforms. Exhaustive cloning revealed the existence of six distinct fibroblastic pro-NDFs, whose basic transmembrane structure includes an immunoglobulin-like motif and an epidermal growth factor (EGF)-like domain. Structural variation is confined to three domains: the C-terminal portion of the EGF-like domain (isoforms alpha and beta), the adjacent juxtamembrane stretch (isoforms 1 to 4), and the variable-length cytoplasmic domain (isoforms a, b, and c). Only certain combinations of the variable domains exist, and they display partial tissue specificity in their expression: pro-NDF-alpha 2 is the predominant form in mesenchymal cells, whereas pro-NDF-beta 1 is the major neuronal isoform. Only the transmembrane isoforms were glycosylated and secreted as biologically active 44-kDa glycoproteins, implying that the transmembrane domain functions as an internal signal peptide. Extensive glycosylation precedes proteolytic cleavage of pro-NDF but has no effect on receptor binding. By contrast, the EGF-like domain fully retains receptor binding activity when expressed separately, but its beta-type C terminus displays higher affinity than alpha-type NDFs. Likewise, structural heterogeneity of the cytoplasmic tails may determine isoform-specific rate of pro-NDF processing. Taken together, these results suggest that different NDF isoforms are generated by alternative splicing and perform distinct tissue-specific functions.

PMID: 7509448 [PubMed - indexed for MEDLINE]